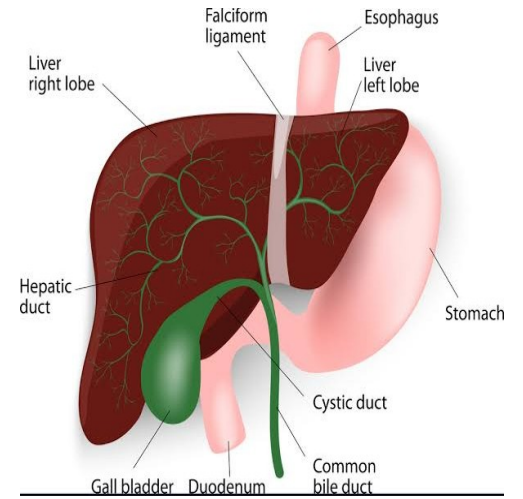




# **Armed Forces College of Medicine AFCM**



# **Physiology of the Liver & Biliary secretions**

**By**

**Mona Gamal El Din Al Anan**

**Ass. Prof. Physiology**

# INTENDED LEARNING OBJECTIVES (ILO)



By the end of this lecture the student will be able to:

1. Explain the major functions of the liver with respect to synthesis, metabolism, detoxification, and excretion of hydrophobic substances
2. Describe entero-hepatic circulation
3. Describe the formation of bile & its constituents
4. Explain its role in the excretion of cholesterol and bilirubin
5. Explain functions of bile salts
6. List functions of gall bladder

# Functions of the liver



Liver is essential for life

It is the most important metabolic organ in the body

The liver & gall bladder are accessory organs of the alimentary tract

# Functions of the liver

## 1- Metabolic function



### 1- Metabolic Function

Carbohydrate  
metabolism

Fat  
metabolism

Protein  
metabolism

# Functions of the liver

## CHO metabolism



The liver plays an important role in

1- Regulation of blood glucose concentrations by either adding or removing glucose from blood according to the body needs (glucostasis)

2 - Converts galactose & fructose into glucose

### I. Well fed state

Glycolysis (ATP)

Glycogenesis  
(glucose storage as glycogen)

Lipogenesis

### II. Fasting state

Glycogenolysis

Gluconeogenesis

# Functions of the liver

## Fat metabolism



### Fat metabolism

**1- Oxidation of fatty acids**  
energy

**2- Synthesis of**

**3- Lipogenesis**

**Cholesterol**  
*(80% is converted to bile salts)*

**lipoproteins**

**phospholipids**

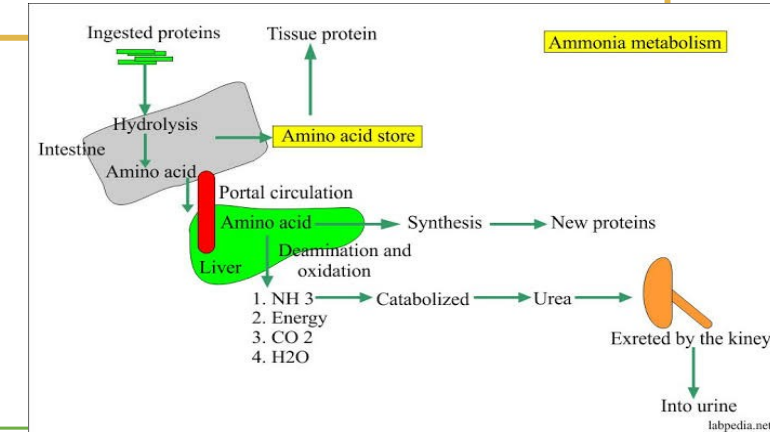
**(fat synthesis from CHO & proteins)**

# Functions of the liver

## Protein metabolism



### Protein metabolism



1- Deamination of amino acids → **ammonia**

2- Transformation of **ammonia** (highly toxic) → **urea** (less toxic) to be excreted in urine

3- Formation of **uric acid** which is the end product of nucleoprotein metabolism

4- Synthesis of **non - essential amino acids**

5- Synthesis of ..... **plasma proteins**



# Functions of the liver

## Protein metabolism

### “Synthesis of ..... plasma proteins”



- **Albumin** is quantitatively the most significant protein synthesized by the liver, and accounts for the majority of plasma oncotic pressure
- Many of the products are **acute-phase proteins**, proteins synthesized & secreted into the plasma on exposure to stressful stimuli
- Others are **proteins that transport steroids and other hormones** in the plasma, and still others are **clotting factors**
- The only major class of plasma proteins not synthesized by the liver are the **immunoglobulins**

**liver failure** □  
**Decreased plasma protein (albumin)** □  
**Decreased oncotic pressure** □  
**edema**

# Functions of the liver

## 2- Formation and secretion of bile



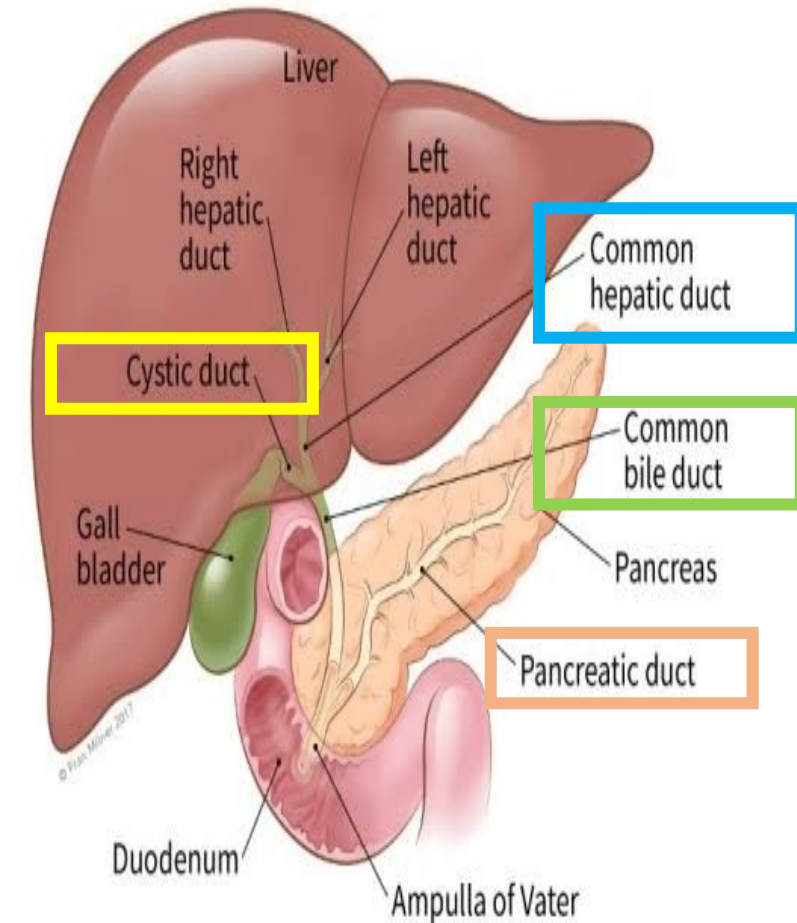
Hepatocytes form & secrete 600-1200 ml/day Bile  
(containing bile salts & bile pigments)

□ bile canaliculi □ Stored in gall bladder □ Emptied into the duodenal lumen with meals

Common hepatic duct + Cystic duct □ Common bile duct (CBD)

Common bile duct (CBD) joins Pancreatic duct

→ forming the ampulla of Vater “opens in duodenum”



# Functions of the liver

## 3- Reservoir function



### Blood reservoir

Liver stores about  
200- 450 ml of blood  
in the hepatic veins  
and sinusoids

This amount can  
replace some of the  
blood lost in  
hemorrhage

# Functions of the liver

## 4 -Detoxification of blood



The liver has  
the ability to  
detoxify &  
excretes  
different  
substances as

Drugs & many  
Toxins

e.g Pencillin,  
erythromycin,  
sulfonamides.

Hormones

e.g  
Aldosterone,  
cortisol,  
thyroxine,,  
estrogen.

Deamination of  
amino acids →  
amonia

Ammonia  
→ urea

Porphyryns  
→ bilirubin

Purines,..  
→ uric acid

# Functions of the liver

## 4 -Detoxification of blood



The liver has the ability to detoxify & excretes different substances as

Drugs & many Toxins

Hormones

Deamination of amino acids → ammonia

In liver failure → increased levels of circulating ammonia → Hepatic encephalopathy

In liver failure → increased levels of drugs →?????

Liver disease can result in the apparent overactivity of some hormones

# Functions of the liver

## 5 - Endocrinal function



### Endocrinal function

Secretes IGF-1 in response to GH  
□ promotes growth

Secretes angiotensinogen to be changed to angiotensin I by renin

Conversion of T<sub>3</sub> to T<sub>4</sub> by deiodination

Activation of vit D<sub>3</sub> then, second activation in kidney □ calcium absorption

Secretes Thrombopoietin □ stimulates platelet production

Secretes Erythropoietin □ stimulates RBCs production

# Functions of the liver



## 6 - The liver is important for erythropoiesis

Liver is important for erythropoiesis

Forms 10% of erythropoietin

Synthesizes the globin part of Hb

Stores vitamin B12

Stores iron  
"Blood iron buffer function"

Stores copper

Erythrocytes formed in liver during fetal life

In Liver Failure □ anemia is a common finding in patients

# Functions of the liver



## 7- The liver is important for blood clotting as it

### Importance of liver for blood clotting

The liver is the only site for formation of

Fibrinogen,

Prothrombin

Factor VIII

**In the presence of vitamin K,**  
Activation of factors

II , VII,  
IX & X

In Liver Failure □ Bleeding tendency is a common finding



# Functions of the liver

## 8 - Storage function



The liver stores

Glycogen

Fat

Vitamins  
(A,D &  
B12) (can  
prevent  
deficiency  
for 10  
months, 3-  
4 months,  
12 months  
respective  
ly)

Iron

Copper

# Functions of the liver

9 - Cleansing function (blood filtration)

10 - Production of acute phase proteins



## Kupffer cells

- Are large phagocytic macrophages that line hepatic sinusoids
- They cleanse & remove 99% of bacteria in the portal blood coming from intestine. *So, in liver failure, systemic infection is common*

In Liver Failure  
systemic  
infection is  
common

## Production of acute phase proteins

- e.g C-reactive protein (important in inflammation)

- List the different functions of liver

# Bile



It is an aqueous, alkaline golden yellow juice that is secreted by the liver & s

- **Volume:** 600-1200 ml/day

- **pH** : alkaline



**Organic constituents (2%)**

**Aqueous, alkaline secretion (97.5%)**



- **Bile salts,**
- **Cholesterol,**
- **Lecithin &**
- **& Bilirubin**

**Secreted by  
hepatocytes**



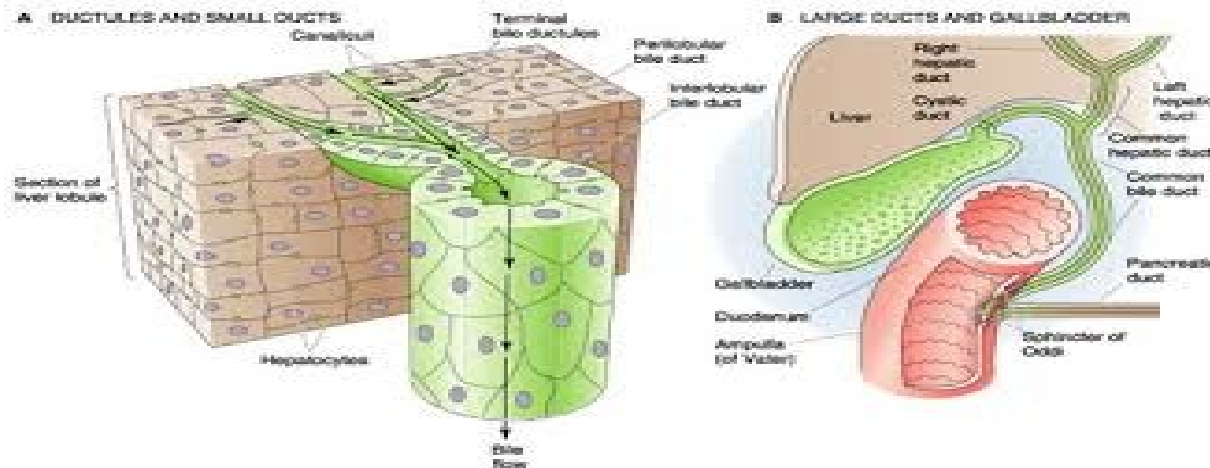
**Watery  
&  
Rich in  $\text{NaHCO}_3$**

**Secreted by  
duct cells**

# Bile formation



## Bile Formation



Copyright © 2005, Elsevier Science (USA). All rights reserved.

**Biliary Tree** --Canaliculi form an extensive meshwork surrounding and draining hepatocytes

Bile from hepatocytes

Small canaliculi

Small terminal ductules (canals of Herring)

Perilobular bile ducts

Interlobular bile ducts

Septal ducts

Cystic duct (gallbladder)

Lobar ducts

Left and right hepatic ducts

Common hepatic bile duct

**COMMON BILE DUCT**

Pancreatic Duct (Ampulla of Vater)

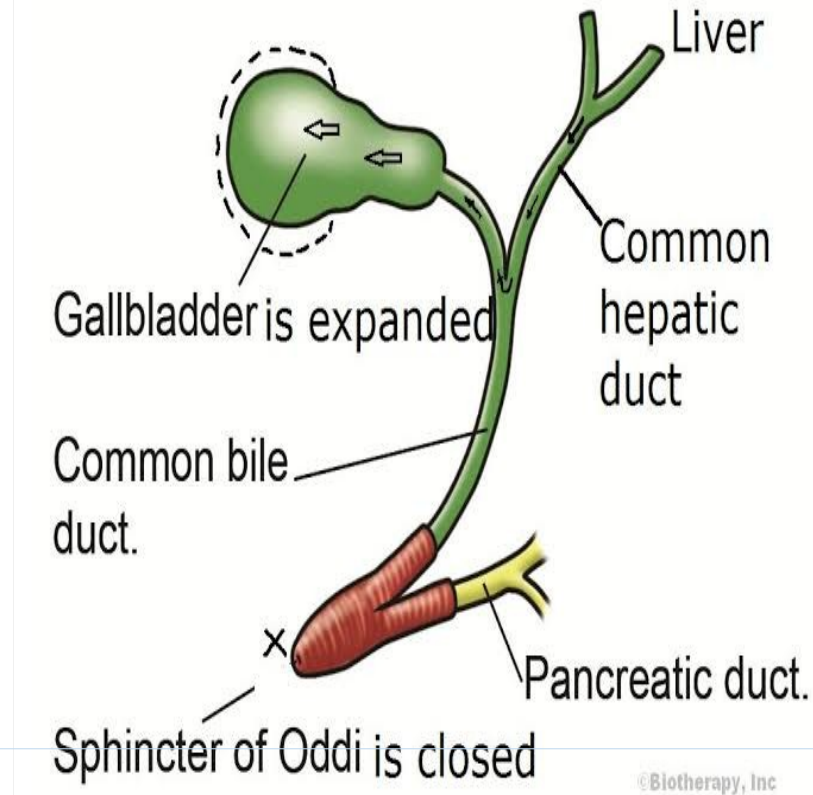
Enters into duodenal lumen at  
Sphincter of Oddi

# Mechanism of bile secretion



## During rest (in between meals)

- Sphincter of Oddi is contracted. So, "secreted bile by the liver passes to be stored in gall bladder "GB"
- GB concentrates bile by active reabsorption of  $\text{Na}^+$  followed by  $\text{Cl}^-$  &  $\text{H}_2\text{O}$  passively



## After meals

- 95% of bile salts are reabsorbed actively from the terminal ileum, then pass into the portal circulation back to the liver

*(Enterohepatic circulation of bile salts)*

## During meals

- Swallowing □ relax sphincter of oddi,
- When food reaches intestine ,CCK □ contraction of GB □ evacuation of bile into duodenum

# Regulation of biliary secretion



## **Chemical** **Bile salts**

The most important stimulant of bile secretion by liver cells

## **Hormonal** Secretin CCK

## **Neural**

Vagal stimulation during the cephalic and gastric phase of gastric secretion □

\* Increases bile secretion rich in  $H_2O$  &  $HCO_3^-$

\* Contraction of gall bladder by releasing acetylcholine & Relaxation of sphincter of oddi

# Regulation of biliary secretion



## Hormonal

### Secretin

Secreted by intestinal mucosa in response to acid chyme

It stimulates bile secretion rich in  $H_2O$  &  $HCO_3$

It is a cholagogue

### CCK

Also Gastrin & Motilin  $\uparrow$  bile secretion

Secreted by intestinal mucosa in response to Fatty acids & Amino acids

It causes strong contraction of GB

It is cholagogue



# Regulation of biliary secretion



## **Choleretic**

Increase bile production (increase water and bicarbonate content of the bile)

**Choleretic**

**2-**

**Secretin**  
**hormone**

Released from S cells of upper intestinal mucosa

**3- Vagus nerve**

**1- Bile salts**  
(most potent)

# Regulation of biliary secretion



## **Cholagogue**

*"Stimulate gall bladder wall contraction and relaxation of sphincter of oddi"*

**Cholagogue**

**1- Cholecystokinin hormone**

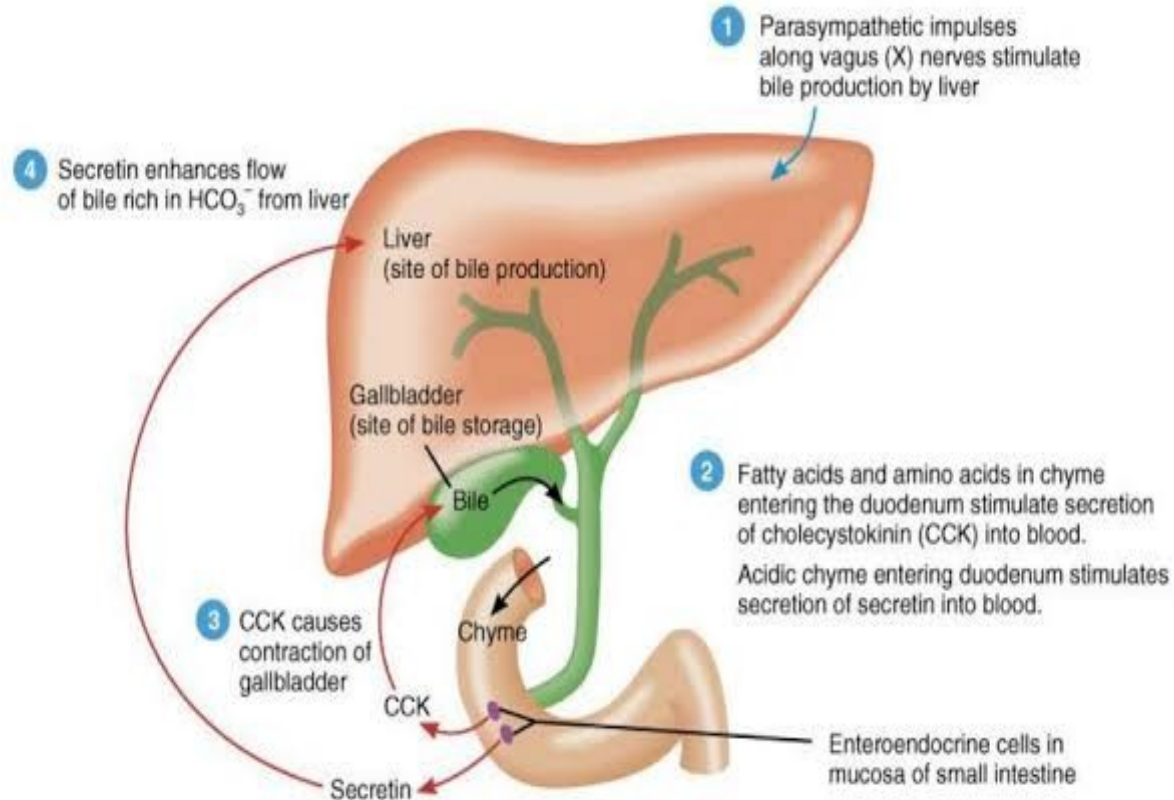
Released from cells of upper intestinal mucosa

**2-vagus nerve**

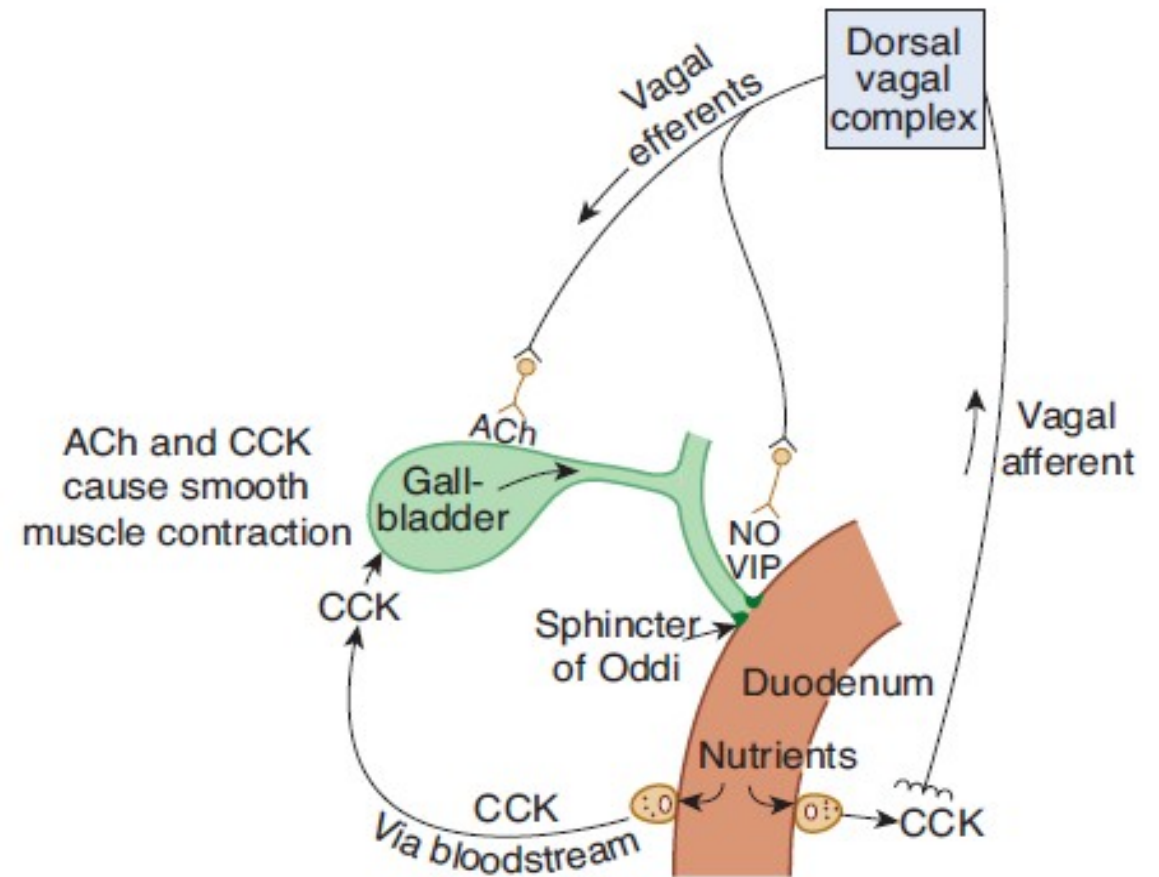
**3- magnesium sulfate**

# Regulation of bile secretion and gall bladder emptying

## Regulation of Bile Secretion



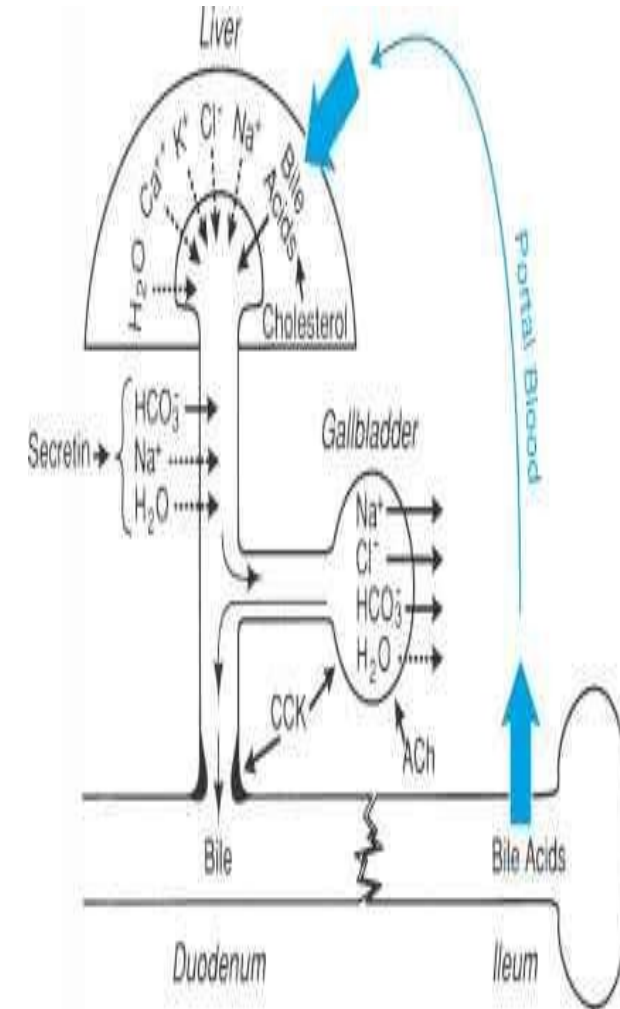
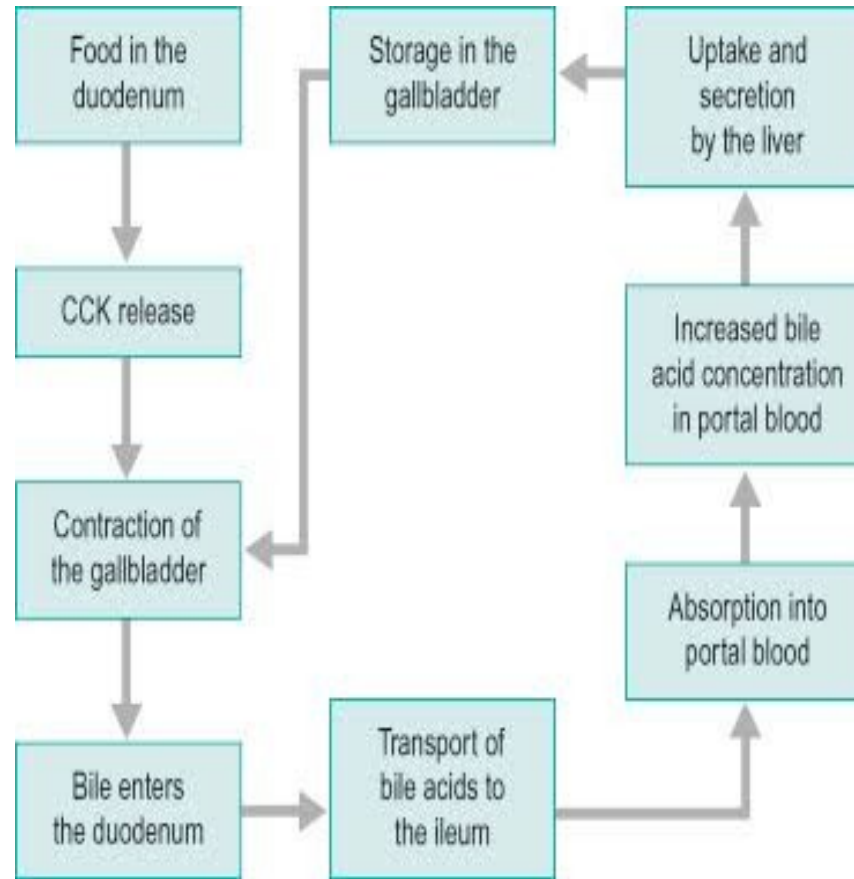
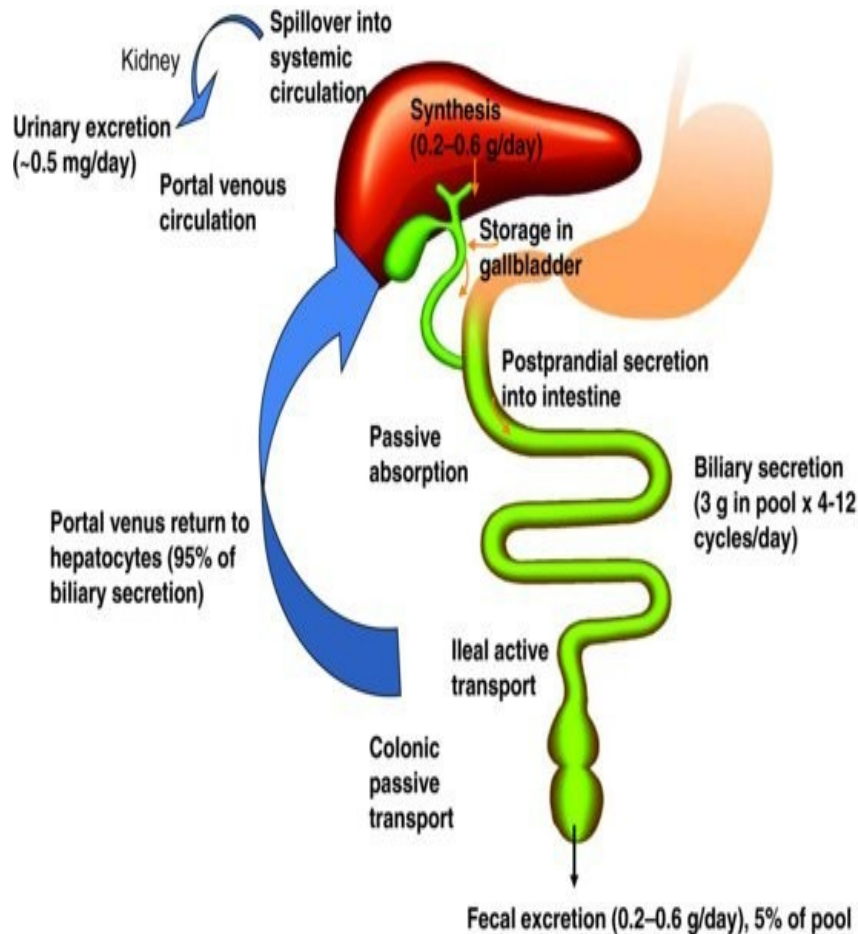
# Neurohumoral control of gallbladder contraction and biliary secretion



<https://encrypted-tbn0.gstatic.com/images?q=tbn%3AANd9GcQOxARqzDzRvQAjzkjPWd8vELyxgsLkq0gOnCu7dg2kBTR9HWKw>

<https://encrypted-tbn0.gstatic.com/images?q=tbn%3AANd9GcS6elqfXDWcfkj2aSBrsC1jCfQgw2rVKUXrdKHt6tQU7Vshuqmb>

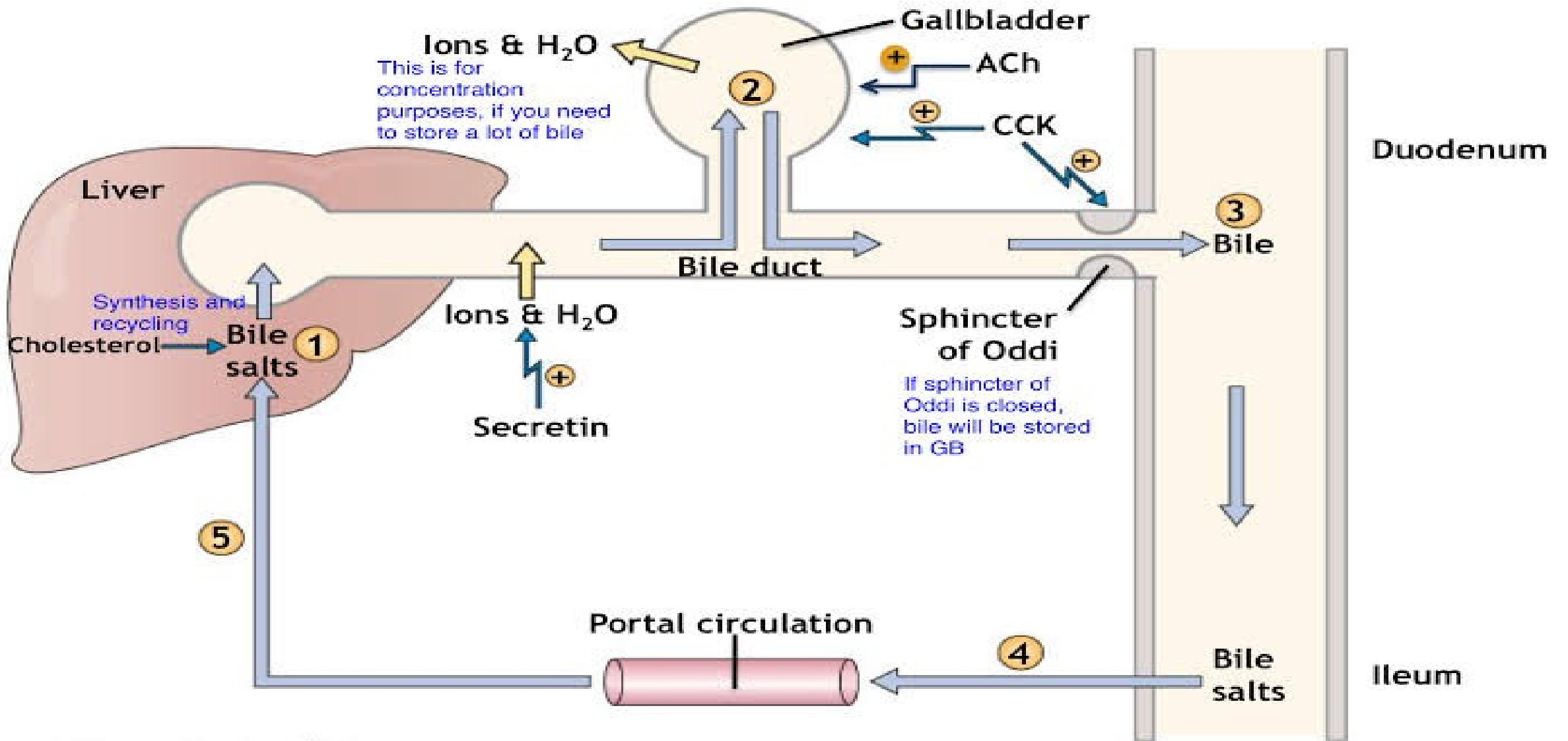
# Enterohepatic circulation of bile salts



[https://www.researchgate.net/profile/John\\_Chiang2/publication/253339735/figure/fig5/AS:271095169286170@1441645533655/Enterohepatic-circulation-of-bile-acids-An-average-man-produces-05g-bile-acid-per-day.png](https://www.researchgate.net/profile/John_Chiang2/publication/253339735/figure/fig5/AS:271095169286170@1441645533655/Enterohepatic-circulation-of-bile-acids-An-average-man-produces-05g-bile-acid-per-day.png)

[https://encrypted-tbn0.gstatic.com/images?q=tbn%3AANd9GcQQhKoHroXcuRBLH\\_0ZRG332dkkbOB0WyCetcYtt0mFwhpv23WG](https://encrypted-tbn0.gstatic.com/images?q=tbn%3AANd9GcQQhKoHroXcuRBLH_0ZRG332dkkbOB0WyCetcYtt0mFwhpv23WG)

**N.B.: 95 % of bile salts are reabsorbed by active transport from the terminal ileum into the blood & the remaining 5-10% enter the colon**





# Functions of bile



Most of the functions of bile are due to the **bile salts**

## 1. DIGESTIVE FUNCTION:-

- **Bile salts** play an important role in fat digestion. Emulsify large fat particles into smaller ones that can be attacked by lipase (detergent action)

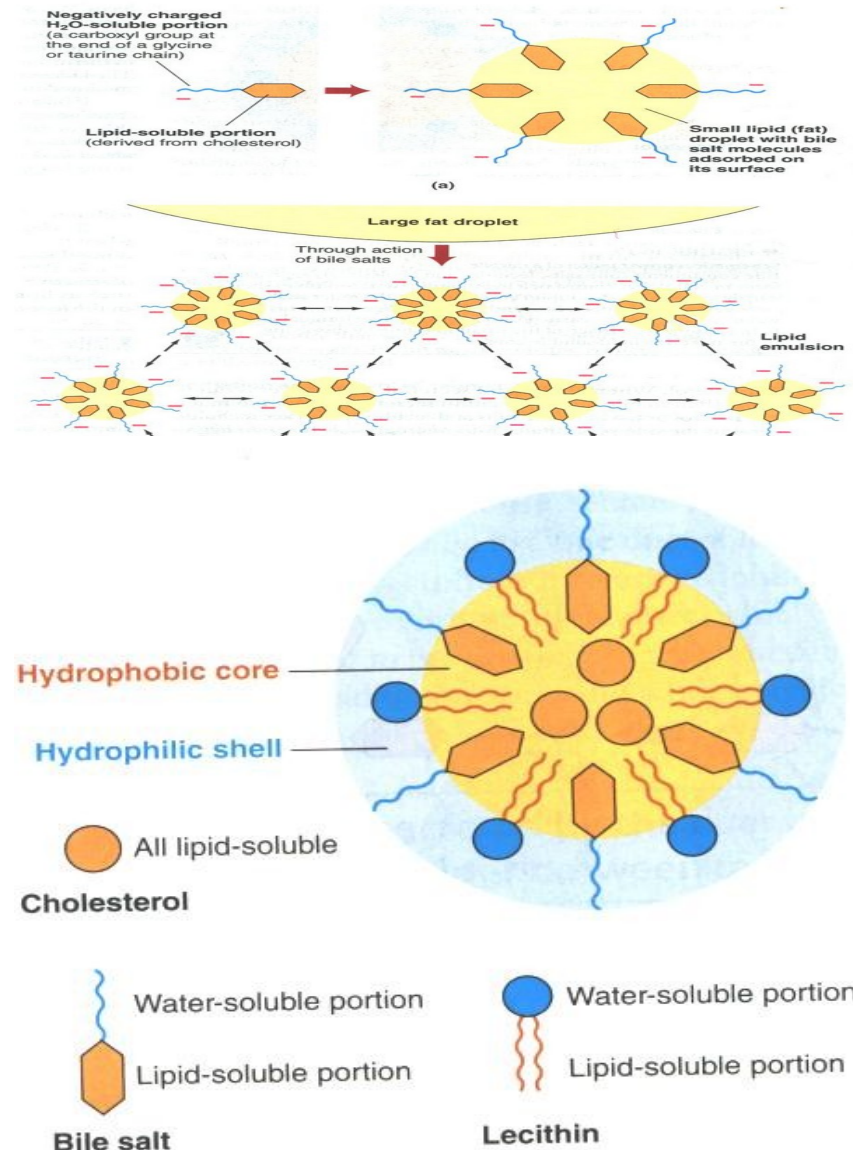
## 2. ABSORPTIVE FUNCTIONS:-

- **Bile salts** play an important role in fat absorption. Help in the transport and absorption of fat (micellar formation)

## 3. EXCRETORY FUNCTIONS:-

Bile pigments are the major excretory products of the bile

Other substances excreted in bile are: i. Heavy metals like copper and iron ii. Some bacteria like typhoid bacteria iii. Some toxins iv. Cholesterol v.



# Functions of bile



Most of the functions of bile are due to the **bile salts**

## 4. LAXATIVE ACTION:-

**Bile salts** act as laxatives by stimulating peristaltic movements of the intestine

## 5. ANTISEPTIC ACTION:-

Bile inhibits the growth of certain bacteria in the lumen of intestine by its natural detergent action

## 6. CHOLERETIC ACTION :-

**Bile salts** have the choleretic action = stimulate the secretion of bile from liver

# Functions of bile



Most of the functions of bile are due to the **bile salts**

## 7. MAINTENANCE OF pH IN GASTROINTESTINAL TRACT:-

As bile is highly alkaline “Bicarbonate” , it neutralizes the acid chyme which enters the intestine from stomach. Thus, an optimum pH is maintained for the action of digestive enzymes

## 8. PREVENTION OF GALLSTONE FORMATION.

- **Bile salts** Prevent precipitation of cholesterol by keeping them in solution (prevent gall stones)

## 9. LUBRICATION FUNCTION:-

The mucin in bile acts as a lubricant for the chyme in intestine

## 10. CHOLAGOGUE ACTION:-

**Bile salts** act as cholagogues. It causes contraction of gallbladder and release of bile into the intestine indirectly by stimulating the secretion of hormone cholecystokinin

# Bile secreted from liver is.....

- Not necessary for normal digestion .
- Important for digestion of protein only
- Stored in gall bladder



# Bile secreted from liver is.....

- Not necessary for normal digestion .
- Important for digestion of protein only
- Stored in gall bladder

# Effects of surgical removal of terminal ileum



Surgical removal of terminal ileum

Loss of bile salts in feces and deficiency of bile salts

Failure of digestion and absorption of fat

Increase undigested fat in feces

**steatorrhea**

Failure of absorption of fat soluble vitamins

Decrease vit K absorption

Decrease clotting factors

**bleeding**

Decrease vit D absorption

Decrease calcium in blood

PTH remove calcium from bone

**osteoporosis**

Precipitation of cholesterol in gall bladder

**Gall stones**

# Functions of the gall bladder



## Storage of bile

tonical contraction of sphincter of oddi between meals  
□ Retrograde flow of bile from cystic duct to be stored in GB

## Acidification of bile

$\text{HCO}_3^-$  reabsorption, this prevents  $\text{Ca}^{++}$  precipitation and formation of gall stones

## Evacuation of bile

Contraction of the wall and relax of the sphincter of oddi stimulated by **cck** and **vagus**)

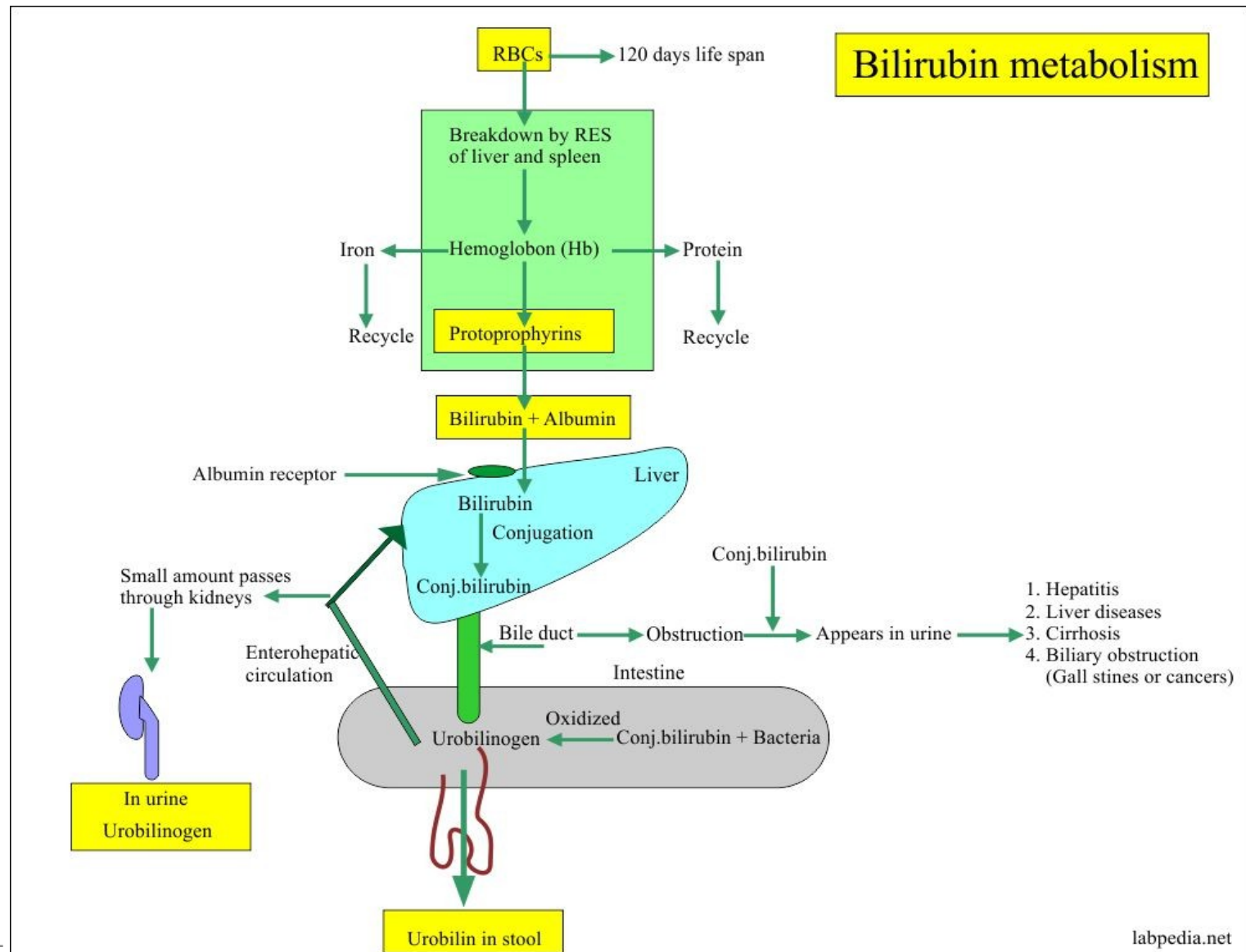
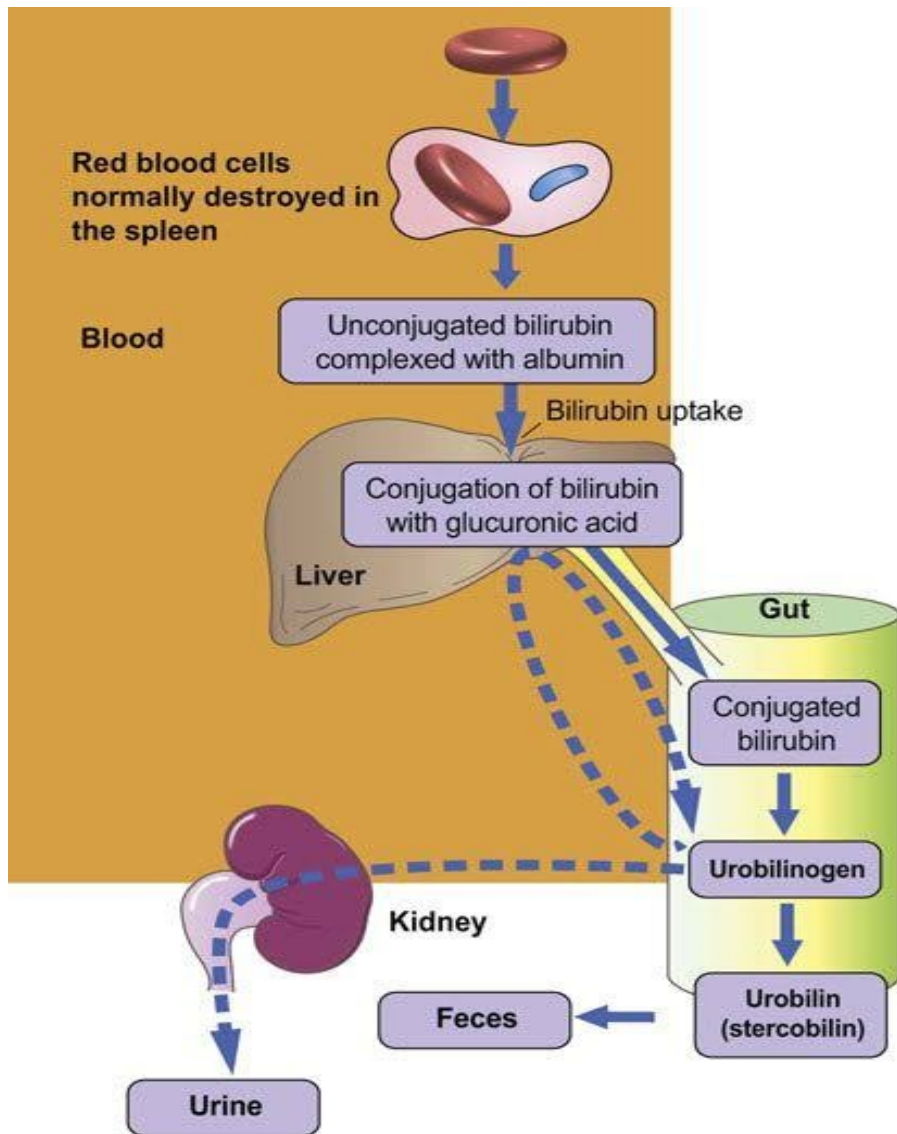
## Concentration of bile

active reabsorption of  $\text{Na}^+$  followed by passive reabsorption of water and most other electrolytes so the conc. of bile salts in GB increased 5-10 times. This concentration of bile prevent the rise in biliary pressure

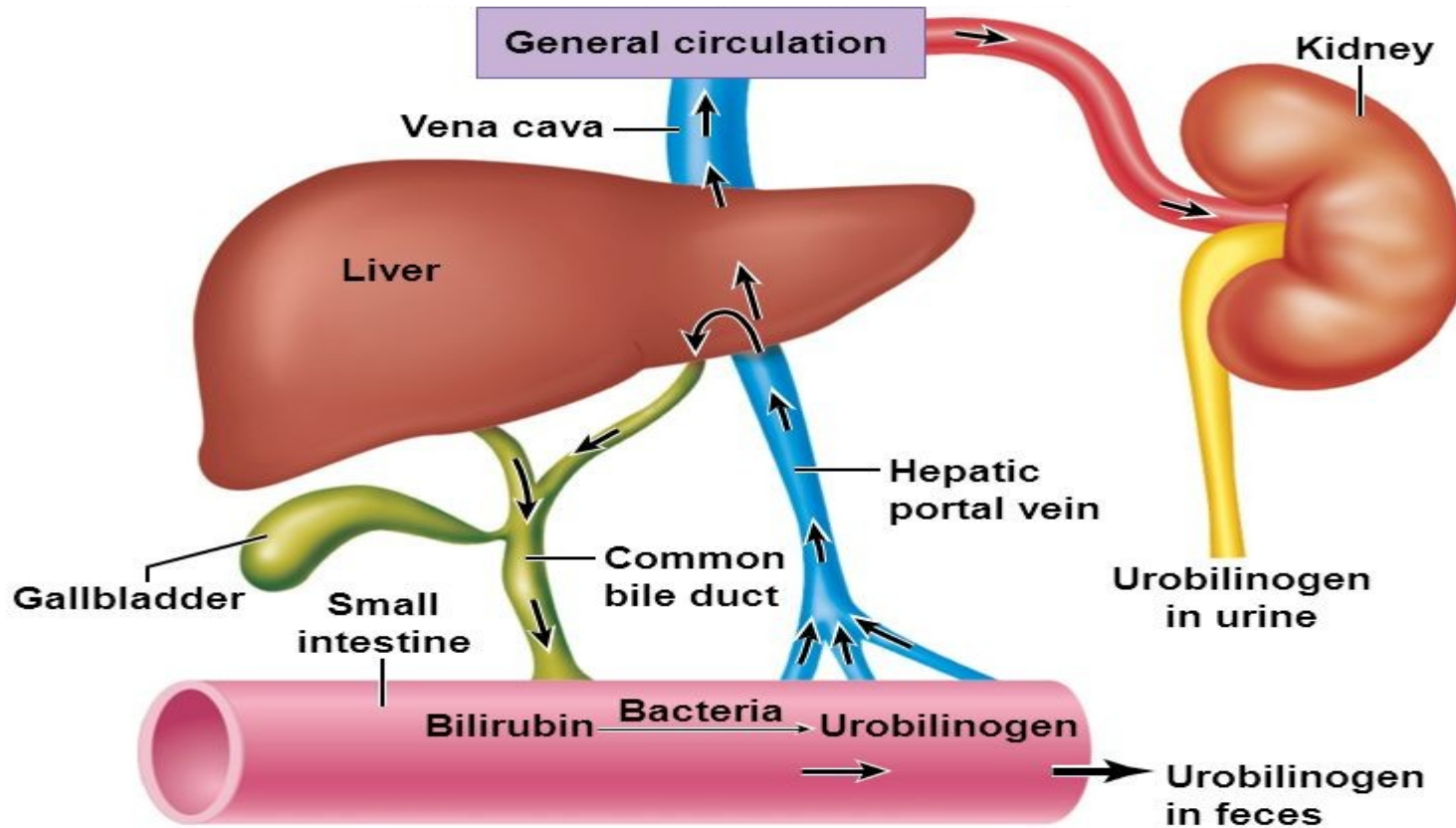
## Secretion of mucus (white bile)

(secreted by GB mucosa protects GB from irritation by acidified concentrated bile, give bile semifluid consistency, in SI act as lubricant and buffer)

# Bile pigments & Bilirubin metabolism



# Enterohepatic circulation of urobilinogen

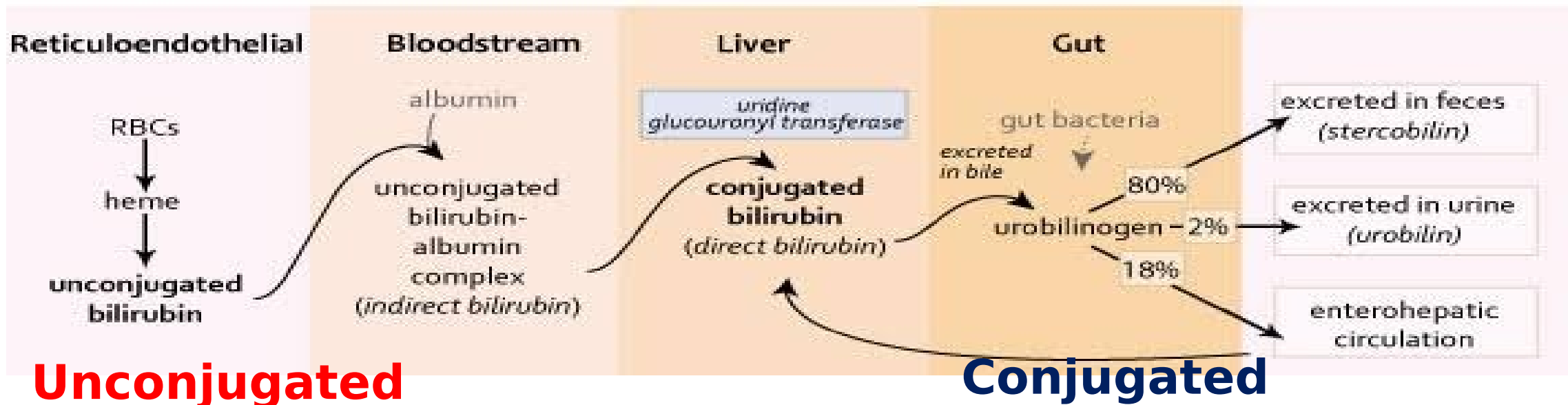


[https://encrypted-tbn0.gstatic.com/images?q=tbn%3AANd9GcQVbK6YFLpOVL3pTZnN\\_9XGwqL5D4ujhTti6HgiM3E7\\_JaXeJK6](https://encrypted-tbn0.gstatic.com/images?q=tbn%3AANd9GcQVbK6YFLpOVL3pTZnN_9XGwqL5D4ujhTti6HgiM3E7_JaXeJK6)

# Bilirubin



## Bilirubin



- Hemobilirubin
- Indirect bilirubin
- Free bilirubin
- Insoluble in water
- Tightly complex to albumin
- Cannot be excreted in urine

- ❖ Cholebilirubin
- ❖ Direct bilirubin
- ❖ Water soluble
- ❖ Loosely bound to albumin
- ❖ Excreted in urine (small amount)





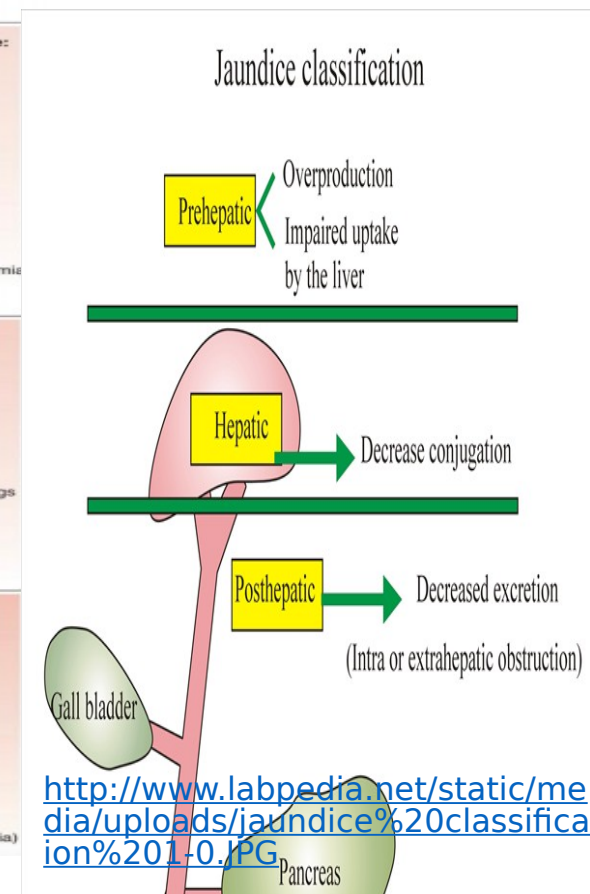
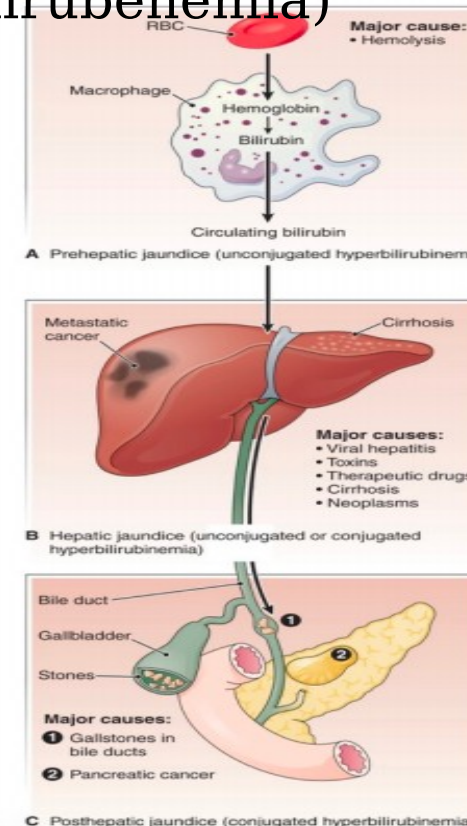
# Jaundice



Yellowish colouration of the skin, eye sclera & mucous membranes due to excessive amounts of bilirubin in the blood  
 plasma bilirubin is **0.5-1.2mg/dl** (almost free bilirubin) - Normal

- Jaundice appears when bilirubin is above **1.5-2 mg/dl**
- Causes: ↑ free bilirubin (unconjugated hyperbilirubinemia) OR

| Category                 | ↑ conjugated bilirubin (conjugated hyperbilirubinemia)                                                                                                      |
|--------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pre-hepatic/hemolytic    | The pathology is occurring prior to the liver, due to either:<br>A. Intrinsic defects in red blood cells<br>B. Extrinsic causes external to red blood cells |
| Hepatic/hepatocellular   | The pathology is located within the liver caused due to disease of parenchymal cells of liver                                                               |
| Post-hepatic/cholestatic | The pathology is located after the conjugation of bilirubin in the liver caused due to obstruction of biliary passage.                                      |



# Jaundice



**Red blood cell destruction**



**Exceed the ability of  
hepatocytes uptake**



**Blood Free Bilirubin  
(Unconjugated)**



**Hemolytic**





# Jaundice

## Liver Diseases



**Conjugation & Excretion of Bilirubin**



**Blood Bilirubin  
(Unconjugated)**



**Hepatic  
Jaundice**

# Jaundice



**Common bile duct Obstruction**



**Bilirubin excretion**



**Blood Bilirubin (Conjugated)**



**Obstructive  
Jaundice**

# Jaundice



|                                           | Haemolytic Jaundice                           | Hepatic Jaundice                                                      | Obstructive Jaundice                                                |
|-------------------------------------------|-----------------------------------------------|-----------------------------------------------------------------------|---------------------------------------------------------------------|
| <b>causes</b>                             | Excessive RBCs break down                     | Liver disease<br>hepatitis , toxic drugs                              | Obstruction of the common bile duct                                 |
| <b>Type of excess bilirubin in plasma</b> | Free bilirubin                                | Free & conjugated bilirubin                                           | Conjugated bilirubin                                                |
| <b>Depth of color</b>                     | Mild                                          | Moderate                                                              | Sever                                                               |
| <b>Fat digestion</b>                      | Normal                                        | Moderately impaired                                                   | Markedly impaired                                                   |
| <b>Liver functions</b>                    | Normal                                        | Markedly impaired                                                     | Moderately impaired                                                 |
| <b>Urine color</b>                        | Normal                                        | Darker than normal                                                    | Dark brown                                                          |
| <b>Stool color</b>                        | Dark                                          | Paler than normal                                                     | Very pale                                                           |
| <b>Blood</b>                              | Anemia, reticulocytosis<br>cause of hemolysis | Moderate increase in cholesterol, alkaline phosphatase and bile salts | Marked increase in cholesterol, alkaline phosphatase and bile salts |

# Liver cell failure



Decreased clotting factors

Bleeding

plasma proteins (albumin)

Edema

liver glycogen

Inability to work

Decreased detoxification of drug

Drug toxicity

Damage to kupffer cell

Systemic infections

Decreased active vitamin D

Osteoporosis

Decreased bile formation

Decreased fat absorption

Decreased conjugation of bilirubin

Jaundice

# Lecture Quiz



**A 43-year-old overweight woman presents to her doctor's office because of right upper quadrant abdominal pain. She has experienced similar episodes of this type of pain in the past and admits that it is worse after meals. Increased secretion of which of the following is responsible for this patient's postprandial pain?**

- a) Cholecystokinin
- b) Decreasing the secretion of gastrin
- c) Pepsin
- d) Somatostatin
- e) Vasoactive intestinal peptide

# Lecture Quiz



**A 43-year-old overweight woman presents to her doctor's office because of right upper quadrant abdominal pain. She has experienced similar episodes of this type of pain in the past and admits that it is worse after meals. Increased secretion of which of the following is responsible for this patient's postprandial pain?**

- a) Cholecystokinin
- b) Decreasing the secretion of gastrin
- c) Pepsin
- d) Somatostatin
- e) Vasoactive intestinal peptide

# SUGGESTED TEXTBOOKS



1. Ganong's "Review of Medical Physiology", 25<sup>th</sup> edition,  
Section V gastrointestinal physiology, Chapter 26
2. Guyton and Hall "Textbook of Medical Physiology", 13<sup>th</sup>  
edition, Chapter 64
3. Sembulingam "Essentials of Medical Physiology", 6<sup>th</sup>  
edition, Chapter 41

